State of California—Health and Human Services Agency
Department of Health Services

California Department of Health Services

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TO: FACILITY ADMINISTRATORS
INFECTION CONTROL PROFESSIONALS

SUBJECT: **Control of Influenza in Long-Term Healthcare Facilities**

Enclosed are the *Recommendations for the Control of Influenza in California Long-Term Care Facilities*, revised for the 2005-2006 influenza season. The most significant changes from the 2004-2005 recommendations are:

- Nursing homes serving Medicare and Medicaid (Medi-Cal) patients now must provide immunizations against influenza and pneumococcal disease to all residents if they want to continue in those programs, according to a federal rule passed on October 7, 2005.

- Standing orders may now be written in California skilled nursing facilities for residents of aged 50 years or older to receive influenza and pneumococcal vaccination, according to Assembly Bill 1711, signed into law in August 2005.

Infection control recommendations in the absence of an outbreak have been added to the recommendations. The vaccine supply this year is anticipated to be sufficient.

CDC now emphasizes that all health-care workers should be vaccinated against influenza annually, and that facilities that employ health-care workers be strongly encouraged to provide vaccine to workers by using approaches that maximize immunization rates. *Please encourage your staff to get vaccinated against the flu and do all that you can to ensure that they do.* The California Adult Immunization Coalition was consists of over 20 organizations committed to developing a long-term, strategic, and integrated effort to improve adult immunization rates for adults who are underserved, at risk and/or have limited access to preventive care services in California. One component of this effort is an initiative to immunize health care workers against influenza. Information and toolkits to assist acute care and long-term care healthcare facilities immunize health care workers is available at the California Adult Immunization Coalition website at: http://immunizecaadults.org/.

Influenza outbreaks occur during the winter months, and as a result, about 2,000 Californians die each year. Influenza is a particularly serious problem in nursing homes where residents are at high risk of developing serious complications or dying due to their age and health problems. Once the influenza virus enters a nursing home, it can spread rapidly. During nursing home outbreaks more than half of the residents can become infected, and some require hospitalization or die. The Department of Health Services and local health departments should be immediately notified of outbreaks of respiratory illness in healthcare facilities. We can provide assistance in: (1) laboratory testing to determine the cause (outbreaks of respiratory illness may be caused by other pathogens); (2) taking measures to control the outbreak, and (3) determining the need for influenza antiviral medications or additional vaccine. California regulations require that any outbreak of illness in a healthcare facility be reported to both the local health department and the Department of Health Services Licensing and Certification district office.

The Department of Health Services encourages facility staff to review these advisory recommendations. Influenza vaccine is available for purchase from a number of providers; if you need help identifying a provider contact your local health department. Questions regarding outbreak control should be referred to your local health department, to Jon Rosenberg M.D., Division of Communicable Disease Control at (510) 620-3427 or to Chris Cahill, at (760) 324 3645 or (415) 710 6489. Written comments about the information contained in these recommendations should be addressed to Dr. Rosenberg, California Department of Health Services, Division of Communicable Disease Control, 850 Marina Bay Parkway, Richmond, CA 94804.

Jon Rosenberg, M.D.
Division of Communicable Disease Control

cc: District Office Managers and Administrators
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Skilled Nursing Facilities
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RECOMMENDATIONS FOR THE PREVENTION, DETECTION, AND CONTROL OF INFLUENZA IN CALIFORNIA LONG-TERM CARE FACILITIES, 2005-2006

This report updates the 2004-2005 recommendations regarding the prevention, detection, and control of influenza outbreaks in California long-term healthcare facilities. These recommendations were developed by the California Department of Health Services, Division of Communicable Disease Control, using information from the Centers for Disease Control and Prevention (CDC), in consultation with the Licensing and Certification Program, and are revised annually. This information is intended to be advisory only and was developed to assist facility infection control committees in the development of a rational approach to the control of influenza in long-term healthcare facilities.

The recommendations are based on the Advisory Committee on Immunization Practices (ACIP), "Prevention and Control of Influenza" (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5408a1.htm). Comprehensive recommendations for immunizations in long-term care facilities "Prevention and Control of Vaccine-Preventable Diseases in Long-Term Care Facilities," are available at (http://www.cdc.gov/nip/publications/Long-term-care.pdf).

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I. What Is Influenza?

Influenza, commonly called "the flu", is a respiratory illness caused by influenza type A or type B viruses. Typical symptoms of influenza include fever, respiratory symptoms (such as cough, sore throat, and other "cold" symptoms), muscle aches and headache. Most young, healthy people who get influenza recover completely within 1-2 weeks. Older people and those with certain chronic diseases are much more likely to develop serious medical complications or die following influenza. Influenza is a particularly serious problem in nursing homes. Because of their age and health problems, nursing home residents are at high risk of developing serious complications or dying when they get influenza. They may also be at high risk of exposure to influenza, since the virus spreads more easily in environments where people live close to each other. Once the virus enters a nursing home, it can spread rapidly. During nursing home outbreaks more than half of the residents may be infected, and many may be hospitalized or die. Influenza typically occurs annually in the winter between October and April; peak activity in a community usually lasts from 6 to 8 weeks, often spanning the New Year period. These recommendations are being issued in anticipation of possible influenza outbreaks in California long-term care facilities this season.

II. What Was the Influenza Season Like in California Last Year?

Overall, influenza activity in the 2004-2005 influenza season was moderate in severity. The magnitude of influenza activity in California was lower than 2003-2004, but comparable to previous years with the exception of the 1999-2000 season. Northern California activity was characterized by two peaks in week 52 of 2004 and weeks 7-9 in 2005. In comparison, Southern California activity was milder overall.

The season was characterized by a large proportion of clinical specimens testing positive for influenza B in California when compared to previous years. A new strain from California was identified, named the A/California/07/2004-like (H3N2) strain, that accounted for the majority of the Type A influenza in the U.S. in 2004-2005. This strain has been included in the 2005-06 influenza vaccine. However, even with optimal matches outbreaks can still occur among vaccinated groups. Information on influenza activity in California can be accessed at http://www.dhs.ca.gov/org/ps/dcdc/VRDL/html/FLU/Fluintro.htm, and for the United States at www.cdc.gov/ncidod/diseases/flu/weeklychoice.htm.

III. How Is Influenza Transmitted?

Influenza is spread from person-to-person by large droplets of respiratory secretions from an infected person. This occurs when infected persons cough, sneeze, or talk, expelling droplets, which are then directly deposited onto the surfaces of the upper respiratory tracts (nose, throat) of susceptible persons who are within 3 feet of the infected person. Transmission also may occur by direct (e.g., person-to-person) or indirect (person-object-person) contact, when a susceptible person picks up the virus on their hands and then touches their nose. Influenza virus can survive for 24-48 hours on nonporous surfaces and 8-12 hours on porous surfaces such as paper or cloth. Airborne transmission, inhalation of small droplets (droplet nuclei) expelled into the air by an infected person coughing, may

also occur. However, this route is probably less important than person-to-person spread by either large droplet or contact transmission.

The most important sources of influenza virus are infected persons. Infected persons are most infectious during the first 3 days of illness; however, they can shed the virus beginning the day before, and up to 7 or more days after, onset of symptoms. Children and severely immunodeficient persons may shed virus for longer periods. In addition, infected but asymptomatic persons can shed the virus and potentially be infectious.

IV. How Can Influenza Be Prevented?

Vaccination is the most effective measure for reducing the illness and deaths from influenza. All residents and staff should be vaccinated against influenza each autumn, beginning in October, before influenza disease is present in the community. **According to a rule passed on October 7, 2005, nursing homes serving Medicare and Medicaid (Medi-Cal) patients must provide immunizations against influenza and pneumococcal disease to all residents if they want to continue in the programs.** Assembly Bill 1711, signed into law in August 2005, removes the prohibition on standing orders in California for residents of skilled nursing facilities aged 50 years or older to receive influenza and pneumococcal vaccination. Skilled nursing facilities should ensure that they comply with the new federal requirements by issuing standing orders for all residents aged 50 years or older to receive annual influenza vaccination and pneumococcal vaccination upon admission. Residents admitted during the winter months should be vaccinated when they are admitted. Information on methods of reimbursement for influenza and pneumococcal vaccine are available from the NIP in "Prevention and Control of Vaccine-Preventable Diseases in Long-Term Care Facilities," accessible at (http://www.cdc.gov/nip/publications/Long-term-care.pdf).

Since the primary source of infection to residents is staff, and the efficacy of vaccination is often reduced in elderly residents, facilities should make a concerted effort to ensure the annual vaccination of staff, also beginning in October. Two recent studies have shown that staff vaccination reduces deaths from respiratory infections in residents.

V. Will There Be Enough Influenza Vaccine This Year?

At the time publication a shortage of vaccine in the United States is not anticipated. However, because of the uncertainties regarding production of influenza vaccine, the exact number of available doses and timing of vaccine distribution for the 2005--06 influenza season remain unknown. Up to date information and recommendations can be obtained at http://www.dhs.ca.gov/ps/dcdc/izgroup/flu.htm and http://www.cdc.gov/flu/. The toll-free CDHS Flu Vaccine Information Line is 866-470-3788. Further information on recommendations for prioritization of vaccination during the 2005--06 influenza season is available http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5434a4.htm.

FluMist ®, the nasal-spray flu vaccine, is an option for healthy individuals, ages 5 to 49 years of age, and may be used as a substitute for standard flu vaccine for healthcare workers in long-term care facilities. FluMist ® is **not** recommended for healthcare workers

taking care of severely immunocompromised people when they are in a protective environment, such as a hospital transplant unit, and cannot be given to pregnant women.

VI. How Is Influenza Diagnosed?

A person with influenza may not appear or feel different than when infected with many other respiratory illnesses that cause fever. However, during outbreaks where influenza has been confirmed through laboratory tests, it can be presumed that other persons with similar symptoms also have influenza. Therefore, **when a cluster of cases of acute febrile respiratory illness occurs it is of critical importance to try to establish the diagnosis through laboratory testing**. **When an outbreak of respiratory illness begins in a nursing home or any healthcare facility, the local health department and Licensing and Certification district office must be notified** (California Code of Regulations Section 72539 and 72541). Health department personnel can provide information about influenza activity in the area and about, diagnostic specimen collection and coordination.

Several commercial rapid diagnostic tests are available that can detect influenza viruses within 30 minutes. Some of these rapid tests detect only influenza A viruses, whereas other rapid tests detect both influenza Type A and B viruses but do not distinguish between the two types. These can be performed on nasopharyngeal-swab or nasal-wash specimens. This information can then be used to begin the use of antiviral drugs to prevent the outbreak from spreading. Precise identification of the strain of virus can be made by growing the virus from nasopharyngeal secretions of acutely ill persons. A rapid antigen test is available in the California Department of Health Services Viral and Rickettsial Disease Laboratory for the investigation of outbreaks.

VII. How is the Spread of Influenza Controlled?

Because transmission of influenza can be controlled with antiviral agents it is important to differentiate the virus that causes influenza A or B from other common respiratory viruses that cause influenza-like illnesses, often defined as an abrupt onset of fever (100° F oral or 101° F rectal) and/or complaints of feverishness with or without myalgia, malaise, headache and at least one of the following respiratory symptoms: cough, sore throat or "cold" symptoms (nasal congestion).

An outbreak is usually defined as an increase in the incidence (number of new cases per time interval) of illness over baseline. However, because influenza is spread so easily in long-term care facilities but may not be diagnosed trough laboratory testing, the occurrence of even a single laboratory confirmed case is considered an outbreak. More than one resident in the facility or an area of the facility (e.g. separate unit) developing an acute febrile respiratory illness during a 1-week period is also considered an outbreak. The Outbreak Management Plan should be activated and outbreak control measures implemented if either one of these occurs.

The local health department should be notified for information about the specific strain of influenza circulating in the community, to help guide the facility medical director to recommend the appropriate antiviral medication, if indicated.

A. Disease Surveillance and Outbreak Management Plan.

Long-term care facilities should develop a surveillance and outbreak control management plan prior to the influenza season and designate a professional to be responsible for continuous disease surveillance for influenza-like illness. A team including the medical director, consulting pharmacist and a representative from the clinical laboratory should assist in developing the plan. Distribute the disease surveillance and outbreak management plan to all admitting physicians requesting confirmation that they agree with the plan. If they do not agree with the plan they should indicate this in writing the facility's medical director and administrator. The plan should include:

1. Consultation with the Centers for Disease Control and Prevention (CDC) and the California Department of Health Services, Immunization Branch (see References and Other Sources of Information, page 11) for annual revisions to influenza vaccination recommendations.
2. Informing new residents, family members, conservators or significant others of the facility's vaccination policy and obtaining a signed consent to vaccinate residents annually.
3. Developing a physician's order form to administer vaccination. This form can be limited to a specific year or can be a blanket consent to vaccinate annually.
   Note: The physician's order form should also request vaccination for *Streptococcus pneumoniae* (pneumococcal pneumonia) at the time of admission. This vaccination is generally given only once in a lifetime. If there is no written documentation of previous immunization or contraindications to vaccination, a vaccination should be given at the time of admission.
4. Maintaining a roster of each resident vaccinated (influenza and pneumococcal) and those who decline vaccination.
5. Developing a vaccination program for staff members. Provide staff written and verbal information on the importance of vaccination and maintain a list of staff members who consent or decline vaccination.
   Note: Educational materials can be obtained from the local health officer or the Department of Health Services, Immunization Branch (see References and Other Sources of Information, page 11).
6. If an influenza outbreak is suspected, offer vaccination to residents and staff who previously declined vaccination.
7. Develop a system for distributing antiviral medication and monitoring for adverse reactions. See Section C, below.
   Note: The medical director should be authorized to order antiviral medication for all residents in the facility.

B. Infection Control Measures for Influenza in the Absence of an Outbreak

Infection control measures can control the spread of influenza and prevent outbreaks. The following measures are recommended to prevent person-to-person transmission of influenza:

1. Respiratory Hygiene/Cough Etiquette Programs
   Respiratory hygiene/cough etiquette should be implemented whenever residents or visitors have symptoms of respiratory infection to prevent the transmission of all

respiratory tract infections in long-term care facilities. Respiratory hygiene/cough etiquette programs include:

- Posting visual alerts instructing residents and persons who accompany them to inform health-care personnel if they have symptoms of respiratory infection and discouraging those who are ill from visiting the facility.
- Providing tissues or masks to residents and visitors who are coughing or sneezing so that they can cover their mouth and nose.
- Ensuring that supplies for handwashing are available where sinks are located and providing dispensers of alcohol-based hand rubs in other locations.
- Encouraging coughing persons to sit at least 3 feet away from others, when possible. Residents with respiratory symptoms should be discouraged from using common areas where feasible.

2. Standard Precautions
   During the care of any resident with symptoms of a respiratory infection, health-care personnel should adhere to Standard Precautions:

   - Wear gloves if hand contact with respiratory secretions or potentially contaminated surfaces is anticipated.
   - Wear a gown if soiling of clothes with a resident's respiratory secretions is anticipated.
   - Change gloves and gowns after each resident encounter and perform hand hygiene.
   - Wash or sanitize hands before and after touching the resident, after touching the resident's environment, or after touching the resident's respiratory secretions, whether or not gloves are worn.
   - When hands are visibly soiled or contaminated with respiratory secretions, wash hands with soap (either plain or antimicrobial) and water.
   - If hands are not visibly soiled, use an alcohol-based hand rub for routinely decontaminating hands. Alternatively, wash hands with soap (either plain or antimicrobial) and water.

3. Droplet Precautions
   In addition to Standard Precautions, health-care workers should adhere to Droplet Precautions during the care of a resident with suspected or confirmed influenza:

   - Place resident into a private room. If a private room is not available, place (cohort) suspected influenza residents with other residents suspected of having influenza; cohort confirmed influenza residents with other residents confirmed to have influenza.
   - Wear a surgical or procedure mask upon entering the resident's room or when working within 3 feet of the resident. Remove the mask when leaving the resident's room and dispose of the mask in a waste container.
   - If resident movement or transport is necessary, have the resident wear a surgical or procedure mask, if possible.

4. Restrictions for Ill Visitors and Health-care Personnel

If no or only sporadic influenza activity is in the surrounding community:

- Discourage persons with symptoms of a respiratory infection from visiting residents. Implement this measure through educational activities.
- Monitor health-care personnel for symptoms of respiratory illness and consider removing those with symptoms from duties that involve direct resident contact. If excluded, they should not provide resident care for 5 days after the onset of symptoms.
- Monitor residents for symptoms of respiratory illness.

If widespread influenza activity is occurring in the surrounding community:

- Actively communicate to the public at large (e.g., via public service announcements) and visitors (e.g., via posted notices) that adults with respiratory symptoms should not visit the facility for 5 days and children with symptoms for 7 days following the onset of illness.
- Actively screen unvaccinated health-care personnel for symptoms of respiratory infection and exclude those with symptoms for 5 days following the onset of symptoms.
- Monitor residents for symptoms of respiratory illness to determine need for precautions.

5. Restrictions for Ill Residents

- To maintain the residents' ability to socialize and have access to rehabilitation opportunities during periods when influenza infections are unlikely and no influenza is suspected or confirmed, residents with respiratory symptoms can be permitted to participate in group meals and activities if they can be placed greater than 3 feet from other residents and can perform respiratory hygiene/cough etiquette
- If influenza is suspected in any resident, influenza testing should be done promptly. Confine symptomatic residents with suspected or confirmed influenza to their rooms or group them together in rooms or on one unit (i.e., cohorted) for 5 days following the onset of symptoms. Personnel should work on only one unit, if possible.
- Patients receiving antiviral treatment for influenza should continue to be confined until treatment is completed to prevent the spread of influenza viruses resistant to the antiviral medication.

C. When an Influenza Outbreak is Suspected

1. Each nursing unit should immediately report any resident(s) or staff member(s) with symptoms of influenza-like illness to the infection control practitioner. New cases should be reported and recorded daily using the case log (Appendix 1, page 12).
2. The medical director should be notified.
3. Confine symptomatic residents to their rooms (see Droplet Precautions).
4. Request symptomatic staff to stay home until symptoms have subsided.

5. Discontinue "floating" staff from the affected unit to non-affected units, if possible.
6. Request symptomatic family members to avoid visitation until the incidence of new cases has decreased and the medical director authorizes visitation.
7. Monitor residents who required hospitalization and who die during the outbreak. Determine if the hospitalization or death was related to complications of influenza such as pneumonia or attributed to underlying disease, and document vaccine status and the use of influenza antiviral medications.
8. Notify the local health officer and the Licensing and Certification district office with jurisdiction over your facility.

D. Confirm Diagnosis by Laboratory Testing

- Notify the laboratory prior to sending specimens for processing. The local health department can assist in recommending the appropriate diagnostic laboratory tests. If rapid antigen tests and/or viral cultures are recommended, determine the appropriate laboratory to process the specimens. If an outbreak is suspected or influenza virus is detected from 1 or more specimens, institute influenza control measures as described below.

E. Implement Influenza Outbreak Control Measures

1. **Cohort** infected residents:
   a. Keep suspected or confirmed infected residents in a private room or in a room with other residents with the same symptoms.
   b. Maintain the same staff to resident assignments, if possible.
   c. Limit staff from floating to non-affected nursing unit, if possible.

2. In addition to Standard Precautions place symptomatic residents on **Droplet Precautions**.
   a. Wear a surgical mask when within 3 feet of symptomatic residents or when entering the room occupied by more than one symptomatic resident.
   b. Place a mask over the resident's nose and mouth when leaving the room if transport or movement of resident is necessary.
   c. Wear gloves when contact with respiratory secretions is anticipated.
   d. Decontaminate hands with soap and water after ungloved or gloved contact with articles contaminated with respiratory secretions. Waterless hand hygiene products may be used if gloved or ungloved hands have not had contact with respiratory secretions.
   e. Wear a gown if soiling of clothes with respiratory secretions is anticipated.

3. Cancel or postpone group activities.

4. Limit new admissions until the no new cases have occurred over 1 week. Start a summary log if the outbreak lasts more than 1 week (Appendix 2, page 13). If new admissions are necessary admit resident to a non-infected unit or to a unit that has had no new cases for at least 2 days.

5. Restrict visitors and volunteers.

6. Vaccinate unvaccinated staff and residents if possible, and consult with the local health department to determine if revaccination of staff or residents during the outbreak would be beneficial. Consider the use of antiviral medication (see G. below).

F. Analyze and Report Data

1. Analyze reports submitted by the nursing units daily.
2. Determine the number of new cases occurring daily and weekly until no new cases are identified.
3. Determine the infection attack rates for residents and staff (# of infected residents/total number of vaccinated and total of non-vaccinated residents) and (# total number of infected staff/total number of vaccinated and the total number of non-vaccinated staff).
4. Report data to the quality assurance/infection control committee.
5. Review the disease surveillance and outbreak management plan to determine necessary revisions.
6. Make revisions for implementation during the next influenza year.

G. Antiviral Drugs for the Control of Influenza Outbreaks.

Antiviral drugs for influenza are an important addition to influenza vaccine for the control of influenza outbreaks. While they are not a substitute for vaccination, they should be considered for use when influenza occurs in a population of unvaccinated persons. Four currently licensed agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Amantadine and rimantadine can be used for treatment and prophylaxis of influenza type A. Oseltamivir and zanamivir are effective against both type A or B influenza; Oseltamivir can be used for treatment and prophylaxis while zanamivir approved for treatment but not prophylaxis of influenza. For additional information on anti-influenza drugs see Appendix 4, page 15.

When outbreaks of influenza occur in a long-term care facility, and antiviral prophylaxis of high-risk persons and treatment of cases is undertaken, drug administration should begin as early in the outbreak as possible to reduce transmission. Contingency planning is needed to ensure immediate availability and rapid administration of the drugs. This might include obtaining prior approval from personal physicians for administration of antiviral drugs to residents in the event of an outbreak. Since it is difficult to know in advance how long antiviral drugs will need to be administered, some nursing homes have a policy that also allows facility staff or a consultant to decide when they should be discontinued.

When institutional outbreaks occur, chemoprophylaxis should be administered to all residents - regardless of whether they received influenza vaccine during the previous fall - and should continue for at least 2 weeks or until approximately 1 week after the end of the outbreak. The dosage for each resident should be determined individually. Chemoprophylaxis also can be offered to unvaccinated staff that provide care to persons at high risk. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza A that is not well matched by the vaccine.

To limit the potential transmission of drug-resistant virus during institutional outbreaks, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact as much as possible between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis.

1. Immediately upon confirmation of influenza, consider the use of antivirals prevent further spread of influenza viruses.

    a. Immediately upon confirmation of influenza A, consider the use of amantadine or rimantadine.
        i. Both rimantadine and amantadine are 70 - 90% effective in preventing influenza A when used for prophylaxis. When used prophylactically they should be administered for at least 2 weeks or until approximately 1 week after the last case of ILI. Rimantadine has fewer side effects but is also more expensive than amantadine. Early administration of these medications during influenza A outbreaks has been effective in limiting them.
        ii. Rimantadine and amantadine can be used for treatment of influenza A infections in three to five day regimens. Treatment of influenza A infections with antiviral medications can reduce the number of days of illness and fever by as much as 50%, and reduce further transmission of influenza **if treatment is started within the first 2 days after illness onset.**

    b. Immediately upon confirmation of influenza A or B, consider the use of oseltamivir or zanamivir.
        i. Zanamivir or oseltamivir can be used for the treatment of both, influenza A and B infections. Zanamivir can reduce the duration of influenza symptoms when started **within the first 2 days of illness onset** and is administered as 2 oral inhalations twice a day for 5 days.
        ii. Oseltamivir has been approved for prophylaxis, but community studies of healthy adults indicate that both drugs are about 80-85% effective in preventing influenza illness.

    c. Antivirals may be considered for prophylaxis of nursing home staff who have been vaccinated less than 2 weeks prior to outbreak, or who have not been vaccinated.

    d. Separate symptomatic patients on antiviral treatment from others to the extent possible in the facility to decrease the possibility of transmitting antiviral-resistant influenza.

    e. Monitor adverse reactions to antivirals using the format of Appendix 3, page 14. Side effects can include disturbances of the central nervous system such as, confusion and dizziness as well as gastrointestinal disturbances.

    f. Exercise precaution when administering rimantadine or amantadine to persons with:
        - decreased renal function (adjust the dose based on creatinine clearance)

- liver dysfunction
- seizure disorders

g. Note: For a more detailed description on dosing, drug-drug interactions, side effects and contraindications of the use of anti-influenza drugs, see Appendix 4, page 15. Also consult the package inserts for these drugs.

References and Other Sources of Information

1. Centers for Disease Control and Prevention. Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report (MMWR) July 29 2005, Vol. 54, No. RR-08. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5408a1.htm.

2. Centers for Disease Control and Prevention, National Immunization Program. Prevention and Control of Vaccine-Preventable Diseases in Long-Term Care Facilities. http://www.cdc.gov/nip/publications/Long-term-care.pdf

3. Hospital Infection Control Practices Advisory Committee. Guidelines for Preventing Health-Care-Associated Pneumonia, 2003. http://www.cdc.gov/ncidod/hip/pneumonia/default.htm .

4. Bradley SF, The Long-Term--Care Committee of the Society for Healthcare Epidemiology of America. Prevention of influenza in long-term care facilities. Infect Control Hosp Epidemiol 1999;20:629-37.

5. Centers for Disease Control and Prevention, Influenza Web Site Home Page. http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm.

6. Centers for Disease Control and Prevention, Influenza Vaccine Information for Health Care Personnel. http://www.cdc.gov/ncidod/hip/flu_vac.htm.

7. Centers for Disease Control and Prevention, Detection and Control of Influenza Outbreaks in Acute Care Facilities. http://www.cdc.gov/ncidod/hip/INFECT/flu_acute.htm.

8. Immunization Branch of the California Department of Health Services
http://www.dhs.ca.gov/ps/dcdc/izgroup/index.htm.
Influenza Information http://www.dhs.ca.gov/ps/dcdc/izgroup/flu.htm.
Influenza Pandemic Response Plan. http://www.dhs.ca.gov/ps/dcdc/izgroup/pdf/pandemic.pdf.

9. California Influenza Surveillance Project, Viral and Rickettsial Disease Laboratory Branch, California Department of Health Services http://www.dhs.ca.gov/ps/dcdc/VRDL/html/FLU/Fluintro.htm.

Appendices

Appendix 1. Sample Case Log of Residents with Acute Respiratory Illness and/or Pneumonia

Patient identification			Patient location			Vaccination status		Illness description										Influenza test results		Pneumococcal test Results		Antivirals	Antibiotic	Illness outcomes				
Name	Age	Sex (M/F)	Building	Unit	Room #, Bed designation	Influenza (Y/N)	Pneumococcal (Y/N)	Date onset Illness	Highest temperature	Cough (Y/N)	Malaise (Y/N)	Chest congestion (Y/N)	Purulent sputum (Y/N)	Rhinitis (Y/N)	Sore throat (Y/N)	Pneumonia(Y/N)	CXR confirmed(Y/N)	Rapid antigen (+/-/IND)	Viral culture	Gram stain	Sputum culture	Date started/Date ended	Date started/Date ended	Influenza (Y/N)	Pneumonia (Y/N)	Hospitalized (Y/N)	Days hospitalized	Died (Y/N, if yes, date)

Appendix 2. Sample Summary Log of Acute Respiratory Illness and Pneumonia

From: Month, day, year To: Month, day, year

Enter the number of persons with the indicated symptoms, test results, and illness outcomes, as indicated

Location	Vaccination status of ill persons		Summary of symptoms									Influenza test results		Pneumo coccal test Results		Antibiotics	Antivirals	Illness outcomes				
Area within the facility ((building, wing, unit, etc)	No. vaccinated: influenza	No. vaccinated: PPV	Temp ≥99°F	Cough (	Malaise	Chest congestion	Purulent sputum	Rhinitis	Sore throat	Pneumonia	CXR confirmed	Rapid antigen (+/-/IND)	Viral culture (+/-/IND)	Gram stain (+/-/IND)	Sputum culture (+/-/IND)	On antibiotics	On antivirals	Influenza positive (Y/N)	S. Pneumo positive (Y/N)	Hospitalized	Died in hospital	Died in facility

From Reference 2.

Appendix 3. Sample Line List of Residents with Adverse Reactions to Anti-Influenza Medication

Facility name_____
Infection Control Coordinator_____
Phone Number:_____
Dates: _____

Patient identification			**Patient location**			**Respiratory illness**		**Antiviral drug/dosing**					**Adverse reaction**							**Actions taken**		
Name	**Age**	**Sex (M/F)**	**Building**	**Unit**	**Room#**	**AFRI (Y/N)**	**Date of illness onset**	**Amantadine (A) Rimantadine (R) Oseltamivir (O) Zanamivir (Z)**	**Date antiviral started**	**Dose (mg)**	**Frequency**	**Creatinine**	**Nervous/anxious**	**Confusion**	**Nausea**	**Anorexia**	**Agitation**	**Seizure**	**Other symptom**	**Antiviral discontinued (Y/N)**	**Date discontinued**	**Dose reduced (Y/N0**

From Reference 2.

Appendix 4. Antiviral Drugs

(from Reference 1)

Four licensed influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Amantadine and rimantadine are chemically related antiviral drugs known as adamantanes with activity against influenza A viruses but not influenza B viruses. Amantadine was approved in 1966 for chemoprophylaxis of influenza A (H2N2) infection and was later approved in 1976 for treatment and chemoprophylaxis of influenza type A virus infections among adults and children aged ≥1 years. Rimantadine was approved in 1993 for treatment and chemoprophylaxis of infection among adults and prophylaxis among children. Although rimantadine is approved only for chemoprophylaxis of infection among children, certain experts in the management of influenza consider it appropriate for treatment among children.

Zanamivir and oseltamivir are chemically related antiviral drugs known as neuraminidase inhibitors, which inhibit neuraminidase and have activity against both influenza A and B viruses. Both zanamivir and oseltamivir were approved in 1999 for treating uncomplicated influenza infections. Zanamivir is approved for treating persons aged ≥7 years, and oseltamivir is approved for treatment for persons aged ≥1 years. In 2000, oseltamivir was approved for chemoprophylaxis of influenza among persons aged ≥13 years.

The four drugs differ in terms of their pharmacokinetics, side effects, routes of administration, approved age groups, dosages, and costs. An overview of the indications, use, administration, and known primary side effects of these medications is presented in the following sections. Information contained in this report might not represent FDA approval or approved labeling for the antiviral agents described. Package inserts should be consulted for additional information.

Indications for Use

Treatment

When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day compared with placebo. More clinical data are available concerning the efficacy of zanamivir and oseltamivir for treatment of influenza A infection than for treatment of influenza B infection. However, in vitro data and studies of treatment among mice and ferrets, in addition to clinical studies, have documented that zanamivir and oseltamivir have activity against influenza B viruses.

None of the four antiviral agents has been demonstrated to be effective in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Evidence for the effectiveness of these four antiviral drugs is based principally on studies of patients with uncomplicated influenza. Data are limited and inconclusive concerning the effectiveness of amantadine, rimantadine, zanamivir, and oseltamivir for treatment of influenza among persons at high risk for serious complications of influenza. Fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations compared with adults.

To reduce the emergence of antiviral drug-resistant viruses, amantadine or rimantadine therapy for persons with influenza A illness should be discontinued as soon as clinically warranted, typically after 3--5 days of treatment or within 24--48 hours after the disappearance of signs and symptoms. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

Chemoprophylaxis

Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in the prevention and control of influenza. Both amantadine and rimantadine are indicated for the

chemoprophylaxis of influenza A infection, but not influenza B. Both drugs are approximately 70%--90% effective in preventing illness from influenza A infection. When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and the development of protective antibody against circulating influenza viruses. Therefore, certain persons who take these drugs will develop protective immune responses to circulating influenza viruses. Amantadine and rimantadine do not interfere with the antibody response to the vaccine. Both drugs have been studied extensively among nursing home populations as a component of influenza outbreak control programs, which can limit the spread of influenza within chronic care institutions.

Among the neuraminidase inhibitor antivirals, zanamivir and oseltamivir, only oseltamivir has been approved for prophylaxis, but community studies of healthy adults indicate that both drugs are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%). Both antiviral agents have also been reported to prevent influenza illness among persons given chemoprophylaxis after a household member was diagnosed with influenza. Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited in comparison with the adamantanes. One 6-week study of oseltamivir prophylaxis among nursing home residents reported a 92% reduction in influenza illness. Use of zanamivir has not been reported to impair the immunologic response to influenza vaccine. Data are not available on the efficacy of any of the four antiviral agents in preventing influenza among severely immune compromised persons.

When determining the timing and duration for administering influenza antiviral medications for prophylaxis, factors related to cost, compliance, and potential side effects should be considered. To be maximally effective as prophylaxis, the drug must be taken each day for the duration of influenza activity in the community. However, to be most cost-effective, one study of amantadine or rimantadine prophylaxis reported that the drugs should be taken only during the period of peak influenza activity in a community.

Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun.

Persons at high risk for complications of influenza still can be vaccinated after an outbreak of influenza has begun in a community. However, the development of antibodies in adults after vaccination can take approximately 2 weeks. When influenza vaccine is administered while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccine for the first time can require 6 weeks of prophylaxis (i.e., prophylaxis for 4 weeks after the first dose of vaccine and an additional 2 weeks of prophylaxis after the second dose).

Persons Who Provide Care to Those at High Risk.

To reduce the spread of virus to persons at high risk during community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact include employees of hospitals, clinics, and chronic-care facilities, household members, visiting nurses, and volunteer workers. If an outbreak is caused by a variant strain of influenza that might not be controlled by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status.

Persons Who Have Immune Deficiency.

Chemoprophylaxis can be considered for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV, chiefly those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if chemoprophylaxis is administered.

Other Persons. Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated. Chemoprophylaxis can also be offered to persons who wish to avoid influenza illness. Health-care providers and patients should make this decision on an individual basis.

Table 1. Recommended adult daily dosage of antiviral medication for treatment and prophylaxis

Antiviral agent	Age Group[1]	
	13-64 years	≥65 years
Amantadine[2]		
Treatment Influenza A	100 mg twice daily	≤100 mg/day
Prophylaxis Influenza A	100 mg twice daily	≤100 mg/day
Rimantadine[3]		
Treatment Influenza A	100 mg twice daily	100 mg/day
Prophylaxis Influenza A	100 mg twice daily	100 mg/day
Zanamivir[4]		
Treatment	10 mg twice daily	10 mg twice daily
Oseltamivir[5]		
Treatment	75 mg twice daily	75 mg twice daily
Prophylaxis	75 mg/day	75 mg/day

[1] For ages less than 14 years consult drug package insert.
[2] The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50mL/min/1.73m^2
[3] A reduction in dose to 100mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤10mL/min. Other persons with less severe hepatic or renal dysfunction taking >100mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.
[4] Zanamivir is administered via inhalation using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not approved for prophylaxis.
[5] A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.

Persons Aged ≥65 Years

Amantadine. The daily dosage of amantadine for persons aged ≥65 years should not exceed 100 mg for prophylaxis or treatment, because renal function declines with increasing age. For certain older persons, the dosage should be further reduced.

Rimantadine. Among older persons, the incidence and severity of central nervous system (CNS) side effects are substantially lower among those taking rimantadine at a dosage of 100 mg/day than among those taking amantadine at dosages adjusted for estimated renal clearance. However, chronically ill older persons have had a higher incidence of CNS and gastrointestinal symptoms and serum concentrations two to four times higher than among healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day.
For prophylaxis among persons aged ≥65 years, the recommended dosage is 100 mg/day. For treatment of older persons in the community, a reduction in dosage to 100 mg/day should be considered if they experience side effects when taking a dosage of 200 mg/day. For treatment of older nursing home residents, the dosage of rimantadine should be reduced to 100 mg/day

Zanamivir and Oseltamivir. No reduction in dosage is recommended on the basis of age alone.

Persons with Impaired Renal Function

Amantadine. A reduction in dosage is recommended for patients with creatinine clearance ≤50 mL/min/1.73m^2. Guidelines for amantadine dosage on the basis of creatinine clearance are found in the package insert. Because recommended dosages on the basis of creatinine clearance might provide only an approximation of the optimal dose for a given patient, such persons should be observed carefully for adverse reactions. If necessary, further reduction in the dose or discontinuation of the drug might be indicated because of side effects. Hemodialysis contributes minimally to amantadine clearance.

Rimantadine. A reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance ≤10 mL/min. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including older persons, should be monitored for adverse effects, and either the dosage should be reduced or the drug should be discontinued, if necessary. Hemodialysis contributes minimally to drug clearance.

Zanamivir. Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir, decreases in renal clearance, increases in half-life, and increased systemic exposure to zanamivir were observed. However, a limited number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose. On the basis of these considerations, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild-to-moderate or severe impairment in renal function.

Oseltamivir. Serum concentrations of oseltamivir carboxylate (GS4071), the active metabolite of oseltamivir, increase with declining renal function (*201,204*). For patients with creatinine clearance of 10--30 mL/min (*201*), a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the prophylaxis dosage to 75 mg every other day is recommended. No treatment or prophylaxis dosing recommendations are available for patients undergoing routine renal dialysis treatment

Persons with Liver Disease

Amantadine. No increase in adverse reactions to amantadine has been observed among persons with liver disease. Rare instances of reversible elevation of liver enzymes among patients receiving amantadine have been reported, although a specific relationship between the drug and such changes has not been established.

Rimantadine. A reduction in dosage to 100 mg/day is recommended for persons with severe hepatic dysfunction.

Zanamivir and Oseltamivir. Neither of these medications has been studied among persons with hepatic dysfunction.

Persons with Seizure Disorders

Amantadine. An increased incidence of seizures has been reported among patients with a history of seizure disorders who have received amantadine. Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine.

Rimantadine. Seizures (or seizure-like activity) have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine. The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated.

Zanamivir and Oseltamivir. Seizure events have been reported during postmarketing use of zanamivir and oseltamivir, although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

Route

Amantadine, rimantadine, and oseltamivir are administered orally. Amantadine and rimantadine are available in tablet or syrup form, and oseltamivir is available in capsule or oral suspension form. Zanamivir is available as a dry powder that is self-administered via oral inhalation by using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of correct use of this device.

Pharmacokinetics

Amantadine. Approximately 90% of amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion (*223,251--254*). Thus, renal clearance of amantadine is reduced substantially among persons with renal insufficiency, and dosages might need to be decreased (see Table 1).

Rimantadine. Approximately 75% of rimantadine is metabolized by the liver (*218*). The safety and pharmacokinetics of rimantadine among persons with liver disease have been evaluated only after single-dose administration (*218,255*). In a study of persons with chronic liver disease (the majority with stabilized cirrhosis), no alterations in liver function were observed after a single dose. However, for persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease.

Rimantadine and its metabolites are excreted by the kidneys. The safety and pharmacokinetics of rimantadine among patients with renal insufficiency have been evaluated only after single-dose administration (*218,244*). Further studies are needed to determine multiple-dose pharmacokinetics and the most appropriate dosages for patients with renal insufficiency. In a single-dose study of patients with anuric renal failure, the apparent clearance of rimantadine was approximately 40% lower, and the elimination half-life was approximately 1.6-fold greater than that among healthy persons of the same age (*244)*. Hemodialysis did not contribute to drug clearance. In studies of persons with less severe renal disease, drug clearance was also reduced, and plasma concentrations were higher than those among control patients without renal disease who were the same weight, age, and sex.

Zanamivir. In studies of healthy volunteers, approximately 7%--21% of the orally inhaled zanamivir dose reached the lungs, and 70%--87% was deposited in the oropharynx. Approximately 4%--17% of the total amount of orally inhaled zanamivir is systemically absorbed. Systemically absorbed zanamivir has a half-life of 2.5--5.1 hours and is excreted unchanged in the urine. Unabsorbed drug is excreted in the feces.

Oseltamivir

Approximately 80% of orally administered oseltamivir is absorbed systemically (*204*). Absorbed oseltamivir is metabolized to oseltamivir carboxylate, the active neuraminidase inhibitor, primarily by hepatic esterases. Oseltamivir carboxylate has a half-life of 6--10 hours and is excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway. Unmetabolized oseltamivir also is excreted in the urine by glomerular filtration and tubular secretion.

Side Effects and Adverse Reactions

When considering the use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (Table 1), presence of other medical conditions; indications for use (i.e., prophylaxis or therapy); and the potential for interaction with other medications.

Amantadine and Rimantadine. Both amantadine and rimantadine can cause CNS and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day. However, incidence of CNS side effects (e.g., nervousness, anxiety, insomnia, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine. In a 6-week study of prophylaxis among healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced $\geq$1 CNS symptoms, compared with approximately 13% of those taking the same dosage of amantadine and 4% of those taking placebo. A study of older persons also demonstrated fewer CNS side effects associated with rimantadine compared with amantadine. Gastrointestinal side effects (e.g., nausea and anorexia) occur in approximately 1%--3% of persons taking either drug, compared with 1% of persons receiving the placebo.

Side effects associated with amantadine and rimantadine are usually mild and cease soon after discontinuing the drug. Side effects can diminish or disappear after the first week, despite continued drug ingestion. However, serious side effects have been observed (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures). These more severe side effects have been associated with high plasma drug concentrations and have been observed most often among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders and among older persons who have been taking amantadine as prophylaxis at a dosage of 200 mg/day. Clinical observations and studies have indicated that lowering the dosage of amantadine among these persons reduces the incidence and severity of such side effects (Table 1). In acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported. Because rimantadine has been marketed for a shorter period than amantadine, its safety among certain patient populations (e.g., chronically ill and elderly persons) has been evaluated less frequently. Because amantadine has anticholinergic effects and might cause mydriasis, it should not be used for patients with untreated angle closure glaucoma.

Zanamivir In a study of zanamivir treatment of influenza-like illness among persons with asthma or chronic obstructive pulmonary disease where study medication was administered after using a B2-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a >20% decline in forced expiratory volume in 1 second (FEV1) after treatment. However, in a study of persons with mild or moderate asthma who did not have influenza-like illness, 1 of 13 patients experienced bronchospasm after administration of zanamivir. In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Certain patients had underlying airways disease (e.g., asthma or chronic obstructive pulmonary disease). Because of the risk for serious adverse events and because the efficacy has not been demonstrated among this population, zanamivir is generally not recommended for treatment for patients with underlying airway disease. If physicians decide to prescribe zanamivir to patients with underlying chronic respiratory disease after carefully considering potential risks and benefits, the drug should be used with caution under conditions of proper monitoring and supportive care, including the availability of short-acting bronchodilators. Patients with asthma or chronic obstructive pulmonary disease who use zanamivir are advised to 1) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and 2) stop using zanamivir and contact their physician if they develop difficulty breathing. No clear evidence is available regarding the safety or efficacy of zanamivir for persons with underlying respiratory or cardiac disease or for persons with complications of acute influenza. Allergic reactions, including oropharyngeal or facial edema, have also been reported during postmarketing surveillance.

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and those receiving placebo (i.e., inhaled lactose vehicle alone). The most common adverse events reported by both groups were diarrhea; nausea; sinusitis; nasal signs and symptoms; bronchitis; cough; headache; dizziness; and ear, nose, and throat infections. Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined.

Oseltamivir. Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%). Among children treated with oseltamivir, 14.3% had vomiting, compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect, whereas a limited number of adults enrolled in clinical

treatment trials of oseltamivir discontinued treatment because of these symptoms. Similar types and rates of adverse events were found in studies of oseltamivir prophylaxis. Nausea and vomiting might be less severe if oseltamivir is taken with food.

Use During Pregnancy. No clinical studies have been conducted regarding the safety or efficacy of amantadine, rimantadine, zanamivir, or oseltamivir for pregnant women; only two cases of amantadine use for severe influenza illness during the third trimester have been reported. However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at very high doses. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see package inserts for additional information.

Drug Interactions. Careful observation is advised when amantadine is administered concurrently with drugs that affect CNS, especially CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions. No clinically significant interactions between rimantadine and other drugs have been identified.

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically important drug interactions have been predicted on the basis of in vitro data and data from studies involving rats.

Limited clinical data are available regarding drug inter-actions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential exists for interaction with other agents excreted by this pathway. For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of oseltamivir carboxylate by approximately 50% and a corresponding approximate twofold increase in the plasma levels of oseltamivir carboxylate.

No published data are available concerning the safety or efficacy of using combinations of any of these four influenza antiviral drugs. For more detailed information concerning potential drug interactions for any of these influenza antiviral drugs, package inserts should be consulted.

Antiviral Drug-Resistant Strains of Influenza

Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Drug-resistant viruses can appear in approximately one third of patients when either amantadine or rimantadine is used for therapy. During the course of amantadine or rimantadine therapy, resistant influenza strains can replace sensitive strains within 2--3 days of starting therapy. Resistant viruses have been isolated from persons who live at home or in an institution where other residents are taking or have recently taken amantadine or rimantadine as therapy; however, the frequency with which resistant viruses are transmitted and their impact on efforts to control influenza are unknown. Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than sensitive viruses. The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses. However, a recent report indicated that the frequency of resistance to amantadine and rimantadine may be increasing worldwide.

Persons who have influenza A infection and who are treated with either amantadine or rimantadine can shed sensitive viruses early in the course of treatment and later shed drug-resistant viruses, especially after 5--7 days of therapy. Such persons can benefit from therapy even when resistant viruses emerge.

Development of viral resistance to zanamivir and oseltamivir during treatment has been identified, and recent reports indicate that this might be more frequent than previously suspected. Available diagnostic tests are not optimal for detecting clinical resistance to the neuraminidase inhibitor antiviral drugs, and additional tests are being developed.